

Estudio numérico del efecto plasmónico en nanobarras de oro sometidas a irradiación polarizada para su aplicación en terapia fototérmica

Numerical Study of Plasmonic Effect in Gold Nanorods Subjected to Polarized Irradiation for Application in Photothermal Therapy

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Resumen. La terapia fototérmica con nanopartículas de oro (GNP) es una alternativa para tratar el cáncer. Las nanobarras (GNR) absorben la radiación infrarroja cercana (NIR) proporcionada por una fuente de calor, provocando hipertermia en las células malignas. Los efectos de hipertermia localizada dependen del tamaño (relación de aspecto, AR), la forma y la concentración de las GNP, la polarización del campo eléctrico, la longitud de onda de irradiación y las propiedades del medio. Se presenta un método computacional para medir las secciones transversal y longitudinal de absorción óptica para GNR basado en el calentamiento óptico de la solución acuosa con un láser polarizado NIR de 805 nm y 905 nm. Se realizó un estudio in-silico para la Teoría de Mie, según el efecto de AR y formación de clústeres, con respecto a la polarización del campo eléctrico ($0^\circ - 180^\circ$). A medida que la polarización del campo eléctrico gira hasta 90° , el pico transversal se desplaza hacia el longitudinal. Las concentraciones más bajas dan lugar a gradientes de temperatura más pequeños. Las teorías utilizadas sirven para predecir las condiciones óptimas de irradiación frente a las propiedades de los nanomateriales para la generación de hipertermia y acoplamiento plasmónico.

Palabras Clave. Terapia fototérmica; electromagnetismo computacional; irradiación polarizada; nanobarras de oro; relación de aspecto; aglomeración.

Abstract. Photothermal therapy assisted by gold nanoparticles (GNP) has emerged as an alternative for treating cancer. The nanorods (GNR) play the role of absorbing near-infrared radiation (NIR) provided by a heat source, causing hyperthermia in malignant cells. Localized hyperthermic effects depend on the size (aspect ratio, AR), shape and concentration of GNP, the polarization of the electric field, the irradiation wavelength and medium properties. A computational method is presented for measuring the cross and longitudinal sections of optical absorption for GNR based on optical heating of the aqueous solution of GNR with an 805 nm–905nm NIR polarized laser. In-silico study was conducted based on the finite-element method for Mie theory, regarding the effect of AR and cluster formation, with respect to the electric field polarization ($0^\circ - 180^\circ$). As the polarization of electric field rotates up to 180° , the cross-peak shifts towards the longitudinal one. Lower concentrations result in smaller temperature gradients. The consulted theories allow predicting the optimal irradiation conditions considering the properties of the used nanomaterials for generating hyperthermia state and plasmonic coupling.

Keywords. Photothermal Therapy; Computational Electromagnetism; Polarized Irradiation; Gold Nanorods; Aspect Ratio; Clustering.

I. Introducción

Plasmonic photothermal therapy (PPTT) is based on the transformation of light energy into thermal energy with the purpose of generating apoptosis in tumour cells, minimizing side effects on healthy cells [1], [2]. Thermo-physical properties within the PPTT depend directly on the metallic nanoparticles used, since they have a considerable movement of electrons, which makes them good conductors of the heat provided by the laser (Joule effect) [3], [4]. Heating effect becomes even more important when it is conducted under the incidence of resonance plasmon, where the heat depends on the absorption rate that nanoparticles present in a defined medium [5].

Gold nanoparticles (GNP) as nanorods (GNR) have been one of the key morphologies in the study of therapy [6], [7]. One of the most outstanding characteristics is that they absorb in the near infrared range (NIR, approx. 755 – 1064 nm), being an ionizing radiation that affects living tissues due to heating effects caused by the combined transfer of energy of many photons [8], [9]. These remarkable optical properties of GNR as photothermal agents have made them attractive for PPTT applications, where they were introduced into the tumour as light-absorbing materials to improve the efficiency in transducing energy to heat [2], [10]. Depending on the heat provided, cells can die by apoptosis if they reach a temperature below 50°C, where an intracellular mechanism is activated that programs the controlled death of cells, without damaging the rest of healthy tissue [11], [12]. In addition, hyperthermia in GNR (temperature increase between 41 °C and 48°C) is greater than other morphologies such as nanospheres (GNS), since they present greater heat absorption in the NIR spectral region, which arises directly from the aspect ratio (AR) and the grouping of GNR, versus the state of polarization of electric field [13].

The shape and size of a nanoparticle determine its optical properties. For example, GNR are nanoparticles that have double absorption bands associated with oscillations of surface plasmons along their two main axes [14], [15]. Transverse mode shows a resonance of about 520 nm, which is coincident with the plasmon resonance of spherical particles of the same diameter, while longitudinal mode resonance is redshifted and highly dependent on the aspect ratio and from the clustering of GNR. The presence of these two modes can be clearly seen in the absorbance results at 520 nm and 780 nm [16]. Oscillation of electrons can occur in one of two directions depending on the polarization of incident light. If the oscillation occurs along the long axis, a strong surface plasmon absorption band is induced at the NIR and is called the longitudinal band. When the oscillation occurs along the short axis, a weak absorption band is induced in the visible region and at a wavelength as GNS. That is typically known

as a crossband. While transverse band is insensitive to changes in size, longitudinal band is redshifted to a large extent from visible to NIR region with increasing aspect ratios ($AR = Length/Width$) [2]. Mackey et al. [17], conducted a study of GNR varying AR from 3.40, 3.45 and 3.50. They concluded that the higher the AR of the GNR, the more effective it is for PPTT when irradiated with a NIR laser (808 nm) at 5.8 W/cm², since it presents a better relationship between the total amount of light absorbed and the fraction that is converted to heat. On the other hand, Alfranca et al. [18], proposed a morphological comparison between GNR and gold nanoprisms (NPr), where they evaluated the heating efficiency, thermoablation capacity and cell internalization, after irradiation with a continuous NIR laser (1064 nm) with an output power of 1100 mW, which illuminated the sample with a power per unit area of approximately 3.3 W/cm² for 10 min. The results indicated that GNR have more efficient heating capacity. However, in vitro thermoablation studies showed that NPr are more effective in inducing cell death through photothermal ablation.

Regarding the plasmonic coupling between clusters of GNR, Chen et al. [19], investigated photothermal therapy of individual cancer cells using two-photon-induced uptake, significantly enhanced by GNR clusters, naturally created in cancer cell lysosomes. Numerical simulations were performed under a physical model for clusters of 100 GNR ($AR = 4.25$) without and with plasmonic coupling between GNR. GNR were arranged in random orientations, immersed inside cubes, which represented the aqueous medium (refractive index of 1.33). Numerical results evidenced that the plasmonic coupling between groups, the amount of GNR in the group and the excitation laser wavelength are factors that can improve the photothermal conversion efficiency. Contrary to isolated GNR, which are highly dependent on the size (AR) and the excitation laser wavelength. The temperature increase was greater in the group with plasmonic coupling. This agrees with the reported by Wei An et al. [20] and Soni et al. [21], where the increase in temperature is attributed to the intensity, duration of irradiation and volumetric fraction of the nanoparticles. Lower particle concentrations result in smaller temperature gradients along the direction of laser transfer. The challenge lies in exploring how the electric field polarization affects the irradiation of plasmonic coupled GNR clusters, which not only depend on the GNR concentration and excitation wavelength, but also on the GNR aspect ratio. Gu et al. [22], presented an experimental and numerical study of the effect of GNR clustering on radiation absorption at the NIR. Surface plasmonic resonance (SPR) wavelength changes when GNR are far apart. They found that both the plasmonic wavelength and the maximum absorption efficiency of a single GNR increase linearly with increas-

ing AR. The highest absorption efficiency was achieved when the major axis of GNR was perpendicular to the incident light. The absorption efficiency at the longitudinal SPR wavelength was almost zero, when the major axis of GNR was parallel to the incident light. Therefore, particle clustering should be considered to accurately measure the heat generation of GNR hyperthermia treatments, as well as GNP concentrations and pH levels of suspensions [23], [24]. Manrique-Bedoya *et al.* [25], were able to observe that the largest GNR absorbs the greatest amount of energy, because its resonance wavelength is closest to the laser wavelength. The energy absorbed is highly dependent on the orientation of the nanoparticle with respect to the incident light. The average energy absorbed is calculated by rotating the particle between 0° (long axis along Y) and 90° (long axis along Z).

On the other hand, polarization state influences the plasmonic effect in cylindrical nanoparticles, where an electric field modelled as a monochromatic wave is guided, which is linearly polarized in order to excite the nanoparticle in plasmonic resonances so that the absorption section is in one particular direction that coincides with the diameter (0°) and with the length (90°). Núñez-Leyva *et al.* [26], worked with two orientations for a GNR ($AR = 3 \pm 1$) immersed in an aqueous spherical medium, where it is irradiated with a polarized laser, at 0° and 90° . Spectral absorption was simulated by finite element method (FEM) and investigated the interaction of GNR with electromagnetic radiation in terms of wavelength, polarization state, geometric parameters, and relative orientation.

Since it is highly rigorous experimentally to achieve that the nanoparticles are isolated or that they are all directed in the same position, this study allows to numerically address the plasmonic coupling that occurs in GNR clusters, according to the electric field polarization by means of different angles, the excitation wavelength and varying the AR of the GNR without altering their orientation. Therefore, the purpose of the in-silico study is to analyze the optical response of GNR, and the heat generated by the interaction of GNR with electromagnetic radiation (electric field polarization state and laser wavelength) in terms of AR and formation of clusters, according to Mie Theory. The article contains a theoretical framework that presents the explanations of physical phenomena such as electric field polarization, surface plasmons, and resonance bands. Consecutively, the methodology used in the numerical study, parameters, variables, domains and equations is shown. Finally, the results obtained from the evolution of the absorption spectra are exposed, according to the polarization of the electric field, the direction of propagation and the aspect ratio of the GNR, up to the influence of the formation of clusters in the plasmonic coupling and increase of temperature.

II. Theoretical Framework

For the case of a GNR, it is possible to determine the absorption (σ_{abs}) and scattering (σ_{sca}) cross-section by means of the speed with which the energy of the incident electromagnetic wave is absorbed (W_{abs}) or scattered (W_{sca}) by the nanoparticle:

$$\sigma_{abs} = \frac{W_{abs}}{I_0} \quad (1)$$

$$\sigma_{sca} = \frac{W_{sca}}{I_0} \quad (2)$$

where I_0 is the irradiance at the input of the system. Now, W_{abs} will depend on the speed at which energy is lost in the nanoparticle (Q_{loss}):

$$W_{abs} = \int \int \int Q_{loss} dV \quad (3)$$

The integral in (3) is calculated for the entire volume of GNR. Q_{loss} can be written in terms of the system current ($\vec{J}_T$), the electric field ($\vec{E}$), the magnetic induction ($\vec{B}$) and the magnetic field ($\vec{H}$) using the expression:

$$Q_{loss} = \frac{1}{2} \mathcal{R} \left\{ \vec{J}_T \cdot \vec{E}^* + j\omega \vec{B} \cdot \vec{H}^* \right\} \quad (4)$$

In equation (4) the symbol $*$ denotes complex conjugate, $\mathcal{R}$ is the real part of the expression between braces and j is the pure imaginary. Thus, it is obtained that the absorption cross-section can be written as:

$$\sigma_{loss} = \frac{1}{2I_0} \iiint_V \mathcal{R} \left\{ \vec{J}_T \cdot \vec{E}^* + j\omega \vec{B} \cdot \vec{H}^* \right\} dV \quad (5)$$

In the case of the speed of energy dispersed by scattering, W_{sca} will depend on the energy flux that crosses a certain imaginary surface (S), which surrounds the GNR.

$$W_{sca} = \oint_S \vec{P} \cdot \hat{n} dS \quad (6)$$

Here, $\vec{P}$ is the Poynting vector associated with the propagating electromagnetic wave that has undergone scattering and $\hat{n}$ is the unit normal vector to the surface S . To calculate the surface integral in (6), the time average of the Poynting vector, that is $\langle \vec{P} \rangle = \frac{1}{2} \mathcal{R} \left\{ \vec{E} \times \vec{H}^* \right\}$, then:

$$W_{sca} = \oint_S \frac{1}{2} \mathcal{R} \left\{ \vec{E} \times \vec{H}^* \right\} \cdot \hat{n} dS \quad (7)$$

Thus, from equation (2) we obtain:

$$\sigma_{sca} = \frac{1}{2I_0} \oint_S \mathcal{R} \left\{ \vec{E} \times \vec{H}^* \right\} \cdot \hat{n} dS \quad (8)$$

III. Materials and Methods

The following sections describe the processes and mathematical models used in computational modelling for the optical spectrum of GNR and the change in temperature and heat generated by nanoparticle clusters according to their AR vs. electric field orientation.

A. Computational Modelling for the Optical Spectrum of Gold Nanorods in an Aqueous Medium

For this part of the study, Mie Theory was taken as a reference and the finite element method (FEM) was used for the solution with the physics of wave optics (specifically, electromagnetic with frequency and wavelength domain) of the Comsol Multiphysics® tool, based on the successful results that have been shown to be obtained by various authors [27], [28].

Knowing the dimensions of the GNR manufactured by chemical synthesis, where the transverse and longitudinal axis are approximately 11 ± 2 nm and 49 ± 8 , respectively, it proceeded to establish the input parameters within the model (see Table 1). The domain consists of positioning a refined GNR with hemispherical ends in a spherical medium, with a perfectly matched layer (PML), as a non-reflective boundary condition alternative, that is, eliminating reflections in space. Subsequently, the materials for the GNR and the medium, gold and water, were defined, assigning the refractive index for the application in the model.

The simulated nanostructure as a GNR was parametrically simulated through different sizes by varying the length of the GNR to obtain different aspect ratios and a parametric sweep was also performed through the orientation of the electric field according to the rotation of the polarizer, where the light travels, at different angles: 0° , 15° , 45° , 65° and 90° , see Figure 1, in order to observe the plasmons corresponding to the two characteristic modes, transversal and longitudinal of the GNR. The optical spectra were plotted following Poynting's theorem and the law of conservation of energy, which establishes that the decrease in electromagnetic energy is due to power dissipation in the form of heat (Joule effect) and to the outward flow of the Poynting vector. The absorption and scattering crosssections were modelled with (1) and (2).

The variables applied were: power output of the relative fields ($nrelPoav$), average time ($nx \times ewfd.relPoa vx + ny \times ewfd.relPoavy + nz \times ewfd.relPoavz$), $ewfd$ is the physics used in Comsol (Electromagnetic Waves, Frequency Domain) and the cross-sections that are calculated from the GNR integration methods, one volumetric: $\sigma_{abs} = \text{intop_vol}(ewfd.Qh)/S_{in}$ (total domain of the GNR) and the other, superficial: $\sigma_{sca} = \text{intop_surf}(nrelPoav)/S_{in}$ (i.e. the outer layers of the GNR). The extinction crosssection is $\sigma_{ext} = \sigma_{sca} + \sigma_{abs}$. Polarized electric field was applied for all domains

(GNR and aqueous spherical medium), in conjunction with wave equation, where refractive indices are kept in mind. Initial values for the electric field were 0 V/m for all three Cartesian coordinates. The dispersion boundary condition is calculated with the boundary of the outer PML, that is, the surface of the medium outside, where a type of dispersion wave is taken as a first-order plane wave.

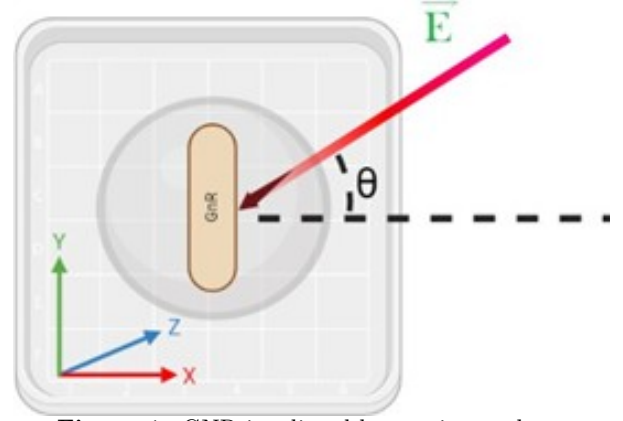


Figure 1. GNR irradiated by continuous laser propagating in the direction of the polarized electric field at different angles.

B. Analysis of the temperature and heat generated by GNR, according to the AR and clustering variables vs. the orientation of the electric field (polarization state)

To obtain the value of heat that a GNR group can generate depending on the concentration and AR, it is necessary to obtain the electromagnetic spectrum for each of the GNR sizes. The size parameters for the nanoparticles and the medium were used, as well as the characteristics of the continuous laser used. Table 2 contains the variables of the mathematical model.

Applied to a 1 ml solution and assuming that there were aggregates of nanoparticles in this, the extinction (9), absorption (10), and scattering (11) solutions optical properties are:

$$\mu_t = \sigma_{ext} \times N \quad (9)$$

$$\mu_a = \sigma_{abs} \times N \quad (10)$$

$$\mu_s = \sigma_{sca} \times N \quad (11)$$

for a given concentration of nanoparticles, N . The predicted heat, described in (12), is defined in terms of the losses that the laser has, $P_{loss} = P_{in} - P_{out} = (1 - \exp(-\mu_t \times L)) \times P_{in}$ and the efficiency, which in

Tabla 1. Parameters and properties for the medium and GNR

Symbol	Units	Concept	Value
a	nm	Nanorod diameter	10
a	nm	Nanorod length	30, 35, 40, 45
AR	–	Nanobar aspect ratio ($R=b/a$)	3.00, 3.50, 4.00, 4.50
k	W/mK	Water conductivity	0.60
N	$1/ml$	Concentration of GNR in solution	1000000, 2500000, 5000000
P_{in}	mW	Experimental input laser power	384
L	nm	Clustering medium length	1.00 [27]
Rf	–	Medium refractive index (Water)	1.33
$E0$	V/m	Initial electric field	1.00
r_{PML}	m	PML Radio	$4.50E-7$
t_{PML}	m	PML thickness	$1.35E-7$
λ_{min}	nm	Minimum wavelength in the scan.	400
λ_{max}	nm	Maximum wavelength in the scan.	1000
λ_{step}	nm	Scan step for wavelength	5
λ	nm	Laser wavelength	905
S_{in}	W/m^2	Incident field energy	0.0013

Tabla 2. Variables of the Mathematical Model

Symbol	Units	Concept
β	–	Thermal capacitance coefficient
μ_t	$1/m$	Solution's extinction coefficient
μ_a	$1/m$	Solution's absorption coefficient
μ_s	$1/m$	Solution's scattering coefficient
Q	mW	Heat generation, approximation
η	–	Thermal conversion efficiency of optical properties
P_{loss}	mW	Lost power
P_{out}	mW	Output power
$\Delta T_{Non-spherical}$	K	Delta temperature for nonspherical nanoparticles

turn depends on the optical properties of the group of nanoparticle, through $\eta = \sigma_{abs}/\sigma_{ext}$.

$$Q = P_{loss} \times \eta = P_{loss} \times \frac{\sigma_{abs}}{\sigma_{ext}} \quad (12)$$

To express the extinction in arbitrary units (a.u), it is necessary to perform a normalization of the values obtained through the procedure described above, using the expression $\sigma_n = (\sigma_i - \sigma_{min})/(\sigma_{max} - \sigma_{min})$, where σ_n is the value for normalized extinction, σ_i the value from Mie theory in m^2 , σ_{min} the minimum value in the data and σ_{max} the maximum value in the data. The calculation of the temperature change for non-spherical particles is done by the expression:

$$\Delta T_{Non-spherical} = \frac{P_{in}}{4\pi k R_{eff} \beta} \quad (13)$$

where β , is determined by the expression $\beta = 1 + 0.96587 \ln^2(b/a)$ [29].

Finally, the calculation for the change in the temperature of the clusters is performed by multiplying the thermal effect of a nanoparticle and the number

of nanoparticles in the cluster, using the following expression, $\Delta T_{cluster} = N \times \Delta T_{Non-spherical}$ [30], taking into account that the average temperature of a tissue $310.15K$ ($37^\circ C$).

IV. Results and Discussion

A. Validation Results

According to G. S. He et al., it is possible to determine the wavelength where the longitudinal peak of the GNR is located with the expression, $\lambda_{max} = 95(AR) + 420$ The value found for the studied ratios can be seen in the [29]. Table 3, coinciding with the values reported in the literature (see Figure 2). For 0° position of the electric field in front of the GNR, it was found that for all AR, the absorption peak will always be found at 510 nm, since the diameter of the GNR was not varied and, furthermore, as light travels in X and is polarized in Y, it is taken as if it were a nanosphere (transverse peak).

B. Effect of AR on Optical Properties

The diameter of the GNR is kept at 10 nm in all the AR used. The planar polarization used is one of the factors that determines the optical behaviour of each of

Tabla 3. Positional, Geometric and Spectral Parameters of GNR in Water

Electric field position ($^{\circ}$)	AR	Absorption peak wavelength (nm)	Absorption peak wavelength G. S. He et al. (nm) [29]
0	3.0, 3.5, 4.0, 4.5	510.0 (transverse peak)	510.0
15, 45, 65, 90	3.0	695.0	—
15, 45, 65, 90	3.5	752.5	750.0
15, 45, 65, 90	4.0	800.0	800.0
15, 45, 65, 90	4.5	847.5	—

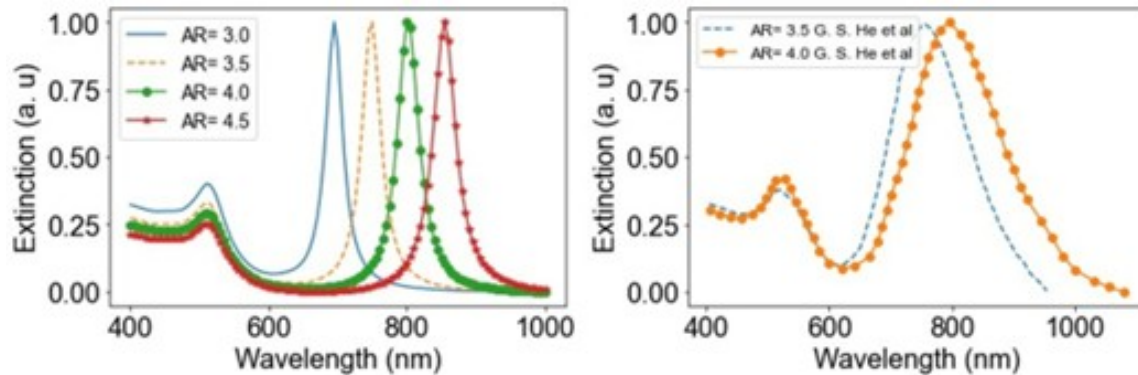


Figure 2. Extinction for AR 3.0, 3.5, 4.0 and 4.5 in arbitrary units (left), compared to the ratios explored by G. S. He et al. (right).

the nanoparticles, thanks to the fact that, by rotating the polarizer, different relative positions of the electric field are obtained (0° , 15° , 45° , 65° and 90°). This effect will have an impact if there is a change in the length of the GNR, thanks to the AR of the cases analysed [29]. The UV-Vis spectrum for the angles or relative positions of the electric field is presented in Figure 3. The optical properties depend directly on the evolution of the positioning of the electric field from 0° to 90° and the increase in the length of the nanorod (change in AR). At the 0° and 90° positions, it can be observed that the maximum wavelength position moves towards the long wavelength side following the increase in AR [29], presenting only the characteristic resonance peak for the diameter size. and the size of the length of the GNR, respectively. This is due to the position adopted by the electric field, with respect to the proposed polarization and propagation. For the rest of positions, there is a combination to a greater or lesser extent between the length and diameter of the GNR, which allows two characteristic attenuation bands to be obtained. For the 0° position of the electric field, there is a scaling in the value of the optical properties depending on AR, between 3.5, 4.0 and 4.5 there is a 12.5% increase in the cross-section of absorption, extinction and scattering. For 15° position, a second peak appears, called longitudinal, which reaches higher values that are positioned around 68% with respect to the transverse peak. This longitudinal peak moves in the electromagnetic spectrum towards the infrared, increasing its wavelength in this optical window. The

transverse peak is at 510 nm, remaining so for the three ratios, the longitudinal peak for the ratio 4.0 presents a displacement of 6.2% and for 4.5 there is a 7% shift towards the infrared with respect to the nanoparticles with a ratio equal to 3.5. The transverse peak begins to disappear at angles from 45° to 90° , with the longitudinal peak being the predominant one, reaching values of $10.94E-15 m^2$, again 68% more than the transverse peak. Similarly, these peaks shift at these angles, the peak resonance length is approximately 750 nm for 3.5, 800 nm for 4.0 and 850 nm for 4.5.

In Figure 4, the change of the spectrum is illustrated against the rotation of the electric field from 0° to 180° due to the effect of polarization, with respect to the proposed AR. This change behaves like a bell shape function, thanks to the fact that symmetry can be observed, with 90° being the peak of the bell for all AR. At this angle, the longitudinal peak is much larger than the transverse peak, at the angles where this peak appears.

Effect of Aspect Ratio and Concentration of GNR on Heat Generation

As mentioned, AR of 3.0, 3.5, 4.0 and 4.5 were used, and concentrations of 1 million NP/ml, 2.5 million NP/ml and 5 million NP/ml, to obtain the heat generated in mW by the nanoparticles under study, see Figure 5. The scaling of the y -axis is done in order to appreciate the increase and decrease of the data in each AR. The laser wavelengths were 805 nm and 905 nm.

For the 905 nm value in the GNR electromagnetic spectrum, the AR of 3.0 generates the lowest heat. On

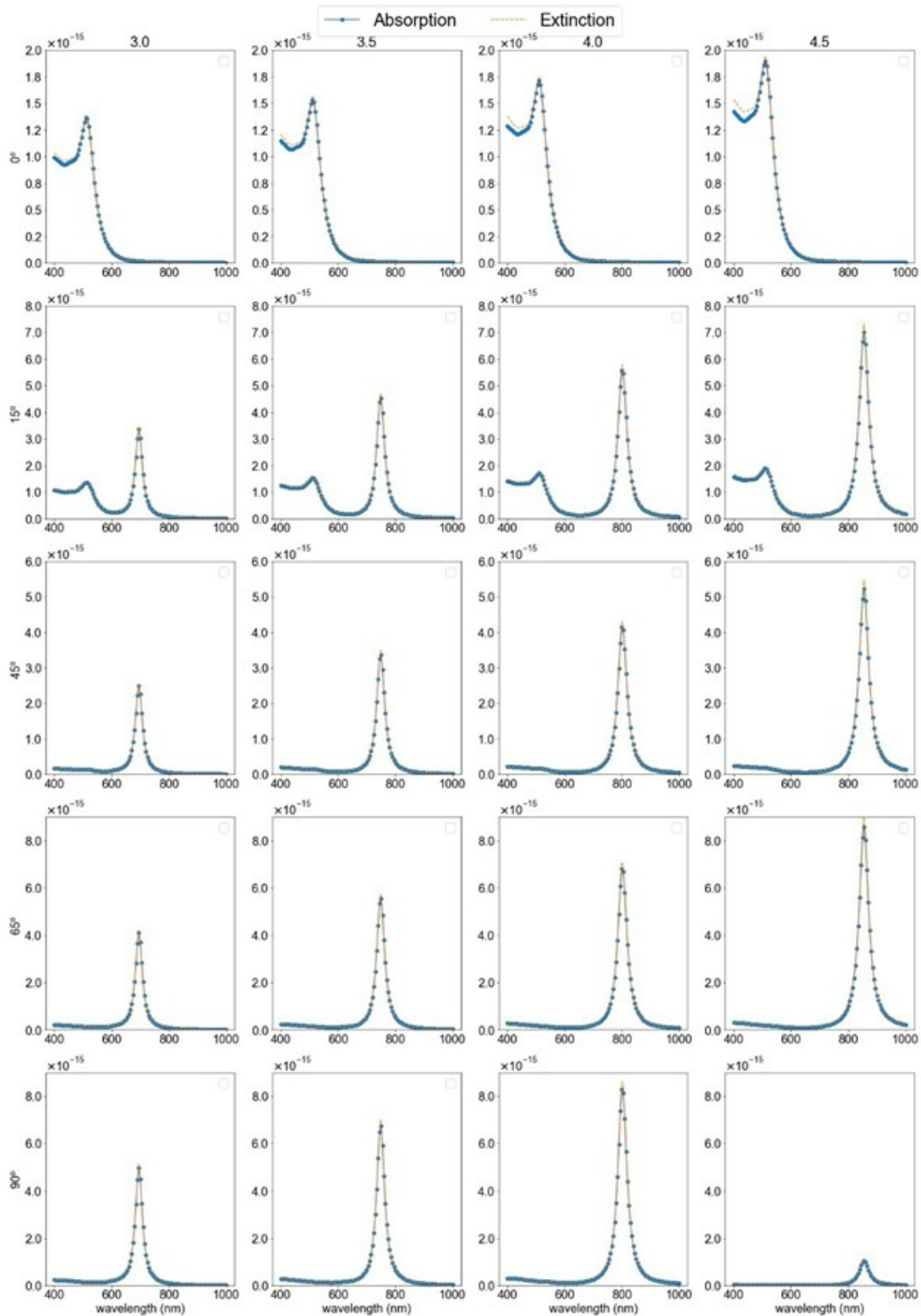


Figure 3. UV-Vis spectrum for the electric field positions: 0°, 15°, 45°, 65° and 90°, at different AR of the GNR. Extinction (—o) and absorption (—), [m²].

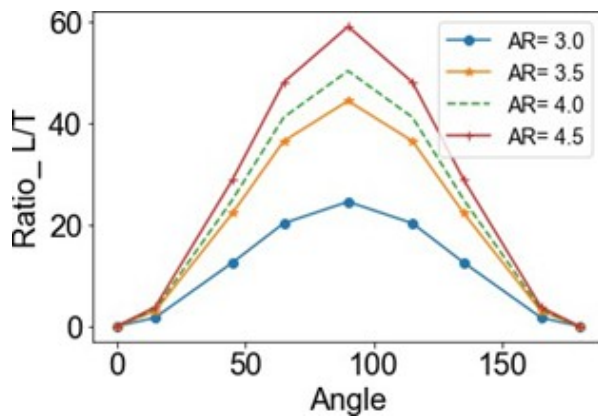


Figure 4. Ratio between longitudinal and transverse peaks as a function of the electric field angle.

the other hand, the AR of 4.5 generates the highest heat among the four ratios studied. The heat generated by the AR 4.5 is 83% greater than that generated by the AR 4.0, an increase of about 5 *mW*, and the AR 3.5 generates 95% less heat than the AR 4.5 (5.7 *mW*), this at a concentration of 1 million NP/ml. The good calorific behavior of the AR of 4.5 is due to the fact that the plasmon resonance wavelength chosen for the irradiation of the nanoparticles coincides with the range where the highest values occur in the longitudinal peak of the UV-Vis spectrum, so that the irradiation coincides with the area where the GNR has its light excitation peak.

As the concentration is increased from 1 million NP/ml to 2.5 million NP/ml, the increase in heat generated for all ratios scales accordingly to the number of nanoparticles added, such that it will be about 2.0 to 2.5 times greater than the generated with 1 million NP/ml, the AR of 4.5 is still the leading ratio for heat generation for the 905 nm wavelength. Similarly, when going from 2.5 million NP/ml to 5 million NP/ml, the heat doubles thanks to the addition of 2.5 million more nanoparticles to the irradiated solution, therefore, the heat generation values will be 2 times higher with respect to the 2.5 million NP/ml and 4.8 times higher with respect to the concentration of 1 million NP/ml.

When testing with the wavelength of 805 nm, it was evidenced that the heat generated with an AR of 4.5 is much less than that observed in an AR of 4.0, the latter being the relationship that generates the most heat of the proven [31]. On the other hand, the generation of AR of 4.5 is greater than the heat generated by AR of 3.0 and 3.5. It is evident that the AR that generates the greatest heat for these nanoparticles is 4.0, with 30 *mW*, for the concentration of 1 million NP/ml, around 28 *mW* more than with the ratio of 3.5. The concentration of 2.5 million NP/ml with an AR of 4.0, generates 60 *mW* and 5 million NP/ml, 120 *mW*.

With the AR taken according to the synthesized GNR, it can be said that for a GNR with an AR of 4.0 that is irradiated at a wavelength of 805 nm, it will have a greater impact on the heat generated, since the peak of the longitudinal band it is at 800 nm and the wavelength is quite close to this value, so much more energy is absorbed. In contrast, a GNR with the same ratios, but irradiated under the incidence of a wavelength of 905 nm, does not reach a considerable increase in heat, since the wavelength does not reach the highest excitation values in the optical spectrum. In fact, the one that comes closest to it for the AR taken was that of 4.5, which has its peak at 850 nm. On the other hand, since the optical window where the longitudinal peak of the AR of 4.5 is located is between 800 nm and 910 nm, the heat generated by the GNR for both wavelengths is similar.

D. Effect on the temperature of a cluster of GNR according to its aspect ratio and concentration

Assuming the body temperature of 37°C as the starting point, for the increase in the temperature of the nanoparticles in the medium, the temperature change produced by the GNR cluster with the concentrations studied, through the model presented, is illustrated in the Figure 6.

The AR with the best performance for this case remains at 4.0, reaching temperatures of 45.85°C for concentrations of 5 million NP/ml, giving an increase of 8.85°C in the temperature of the GNR. The smallest increase is presented by the AR of 3.0, obtaining a maximum of 37.03°C, an increase of 0.03°C. The most important increase for a 905 nm source occurs in the concentration of 5 million NP/ml, for a ratio of 4.5, at 38.45°C, with a growth of 1.45°C.

An ANOVA type statistical analysis was performed in order to find the statistical significance according to the comparison of the wavelengths (805 nm and 905 nm) in each AR and concentration (see Figure 7). The F-ratio, which in this case equals 4.9279 (for AR equals 3.0), 7.2186 (AR equals 3.5), 9.2823 (AR equals 4.0), and 0.0008 (AR equals 4.5) for all concentrations, is the ratio between the between-groups estimate and the withingroups estimate. Since the P-value of the F-test is less than 0.05, there is a statistically significant difference between the means of the 2 variables for each AR and at all concentrations at the 5% level of significance, except for the AR of 4.5 with a 97.77% probability that the data are not significantly different (Table 4).

There is a difference of more than 3 to 1 between the smallest and largest standard deviation. The standardized bias and standardized kurtosis lie within the range of -2 to +2 for all comparisons between irradiation wavelengths at different AR and concentrations.

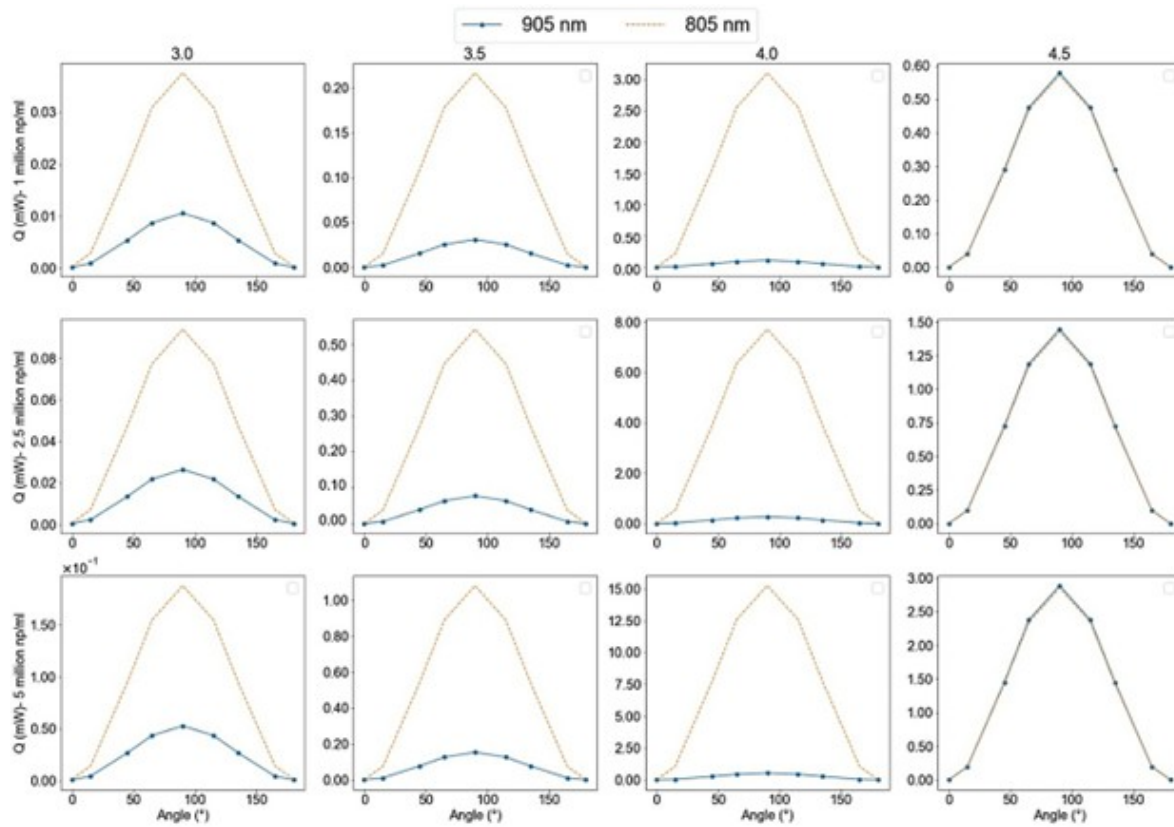


Figure 5. Heat generated for the AR of 3.0, 3.5, 4.0, and 4.5 at the irradiation wavelengths of 805 nm and 905 nm for different GNR concentrations.

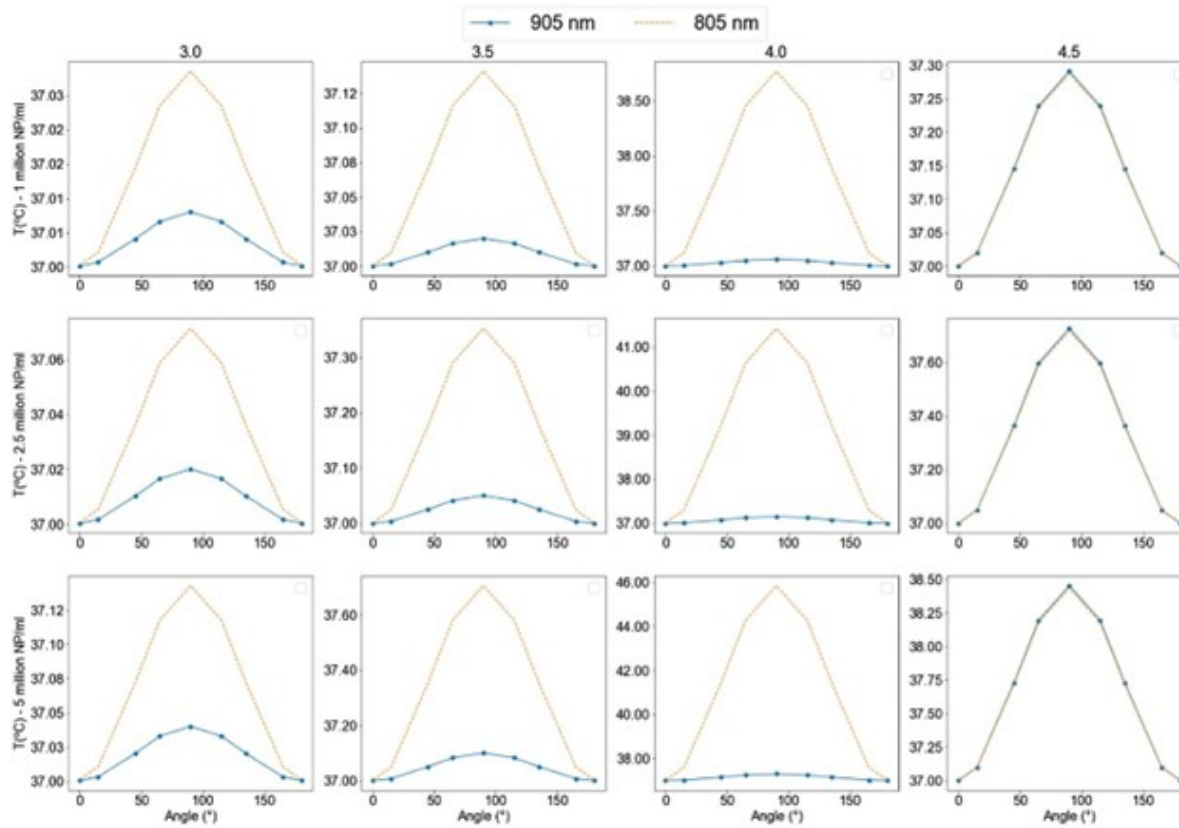


Figure 6. Temperature vs. GNR position at different concentrations.

Tabla 4. Statistical significance according to the comparison of the wavelengths (805 nm and 905 nm) according to ANOVA

Concentration	<i>p</i> -value			
	<i>AR</i> = 3.0	<i>AR</i> = 3.5	<i>AR</i> = 4.0	<i>AR</i> = 4.5
1 million NP/ml				
2.5 million NP/ml	0.0412	0.0162	0.0077	0.9777
5 million NP/ml				

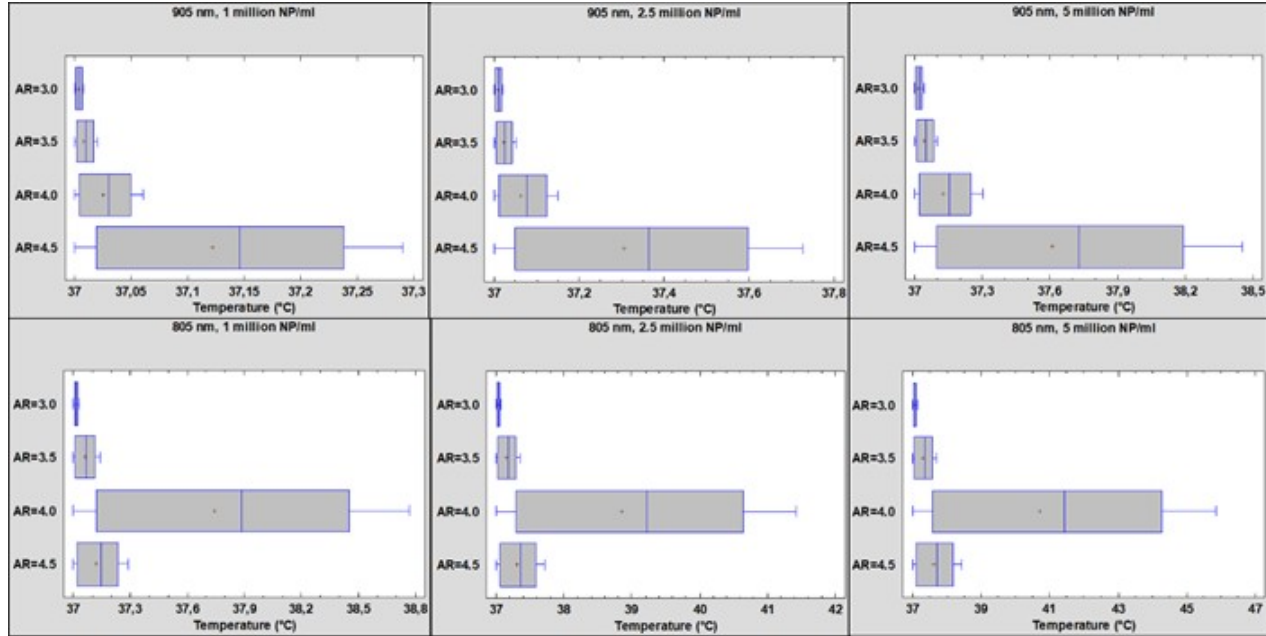


Figure 7. Box-and-whisker plot for wavelengths 805 and 905 nm, accounting for both AR and GNR concentration.

This indicates some significant normality in the data (the data come from normal distributions).

Hyperthermia is only achieved with irradiation under the 805 nm laser, with AR of 4.0 and with concentrations of 2.5 and 5 million NP/ml.

V. Conclusions

The computational study was carried out around the analysis of the optical spectrum for the GNR at different aspect ratios (3.0, 3.5, 4.0 and 4.5), the calculation of the change in temperature and heat generated by clusters with concentrations of 1 million NP/ml, 2.5 million NP/ml and 5 million NP/ml, compared to the change of orientation of the incident electric field. The position of the electric field on the GNR can influence the appearance and the size of the two characteristic peaks. Nanoparticles irradiated with a wavelength of 905 nm were found to require a higher AR, compared to those irradiated at 805 nm, to generate an amount of heat exceeding 5 mW, and to approach hyperthermia values. It is possible to synthesize GNR at different aspect ratios and test the proposed model to acquire a suitable laser, according to the peaks obtained in the optical spectrum. This would allow to control the heat generation by means of the correct tuning between the wavelength of the laser and the aspect ratio of the GNR

(peak of the longitudinal band). Knowing the effect of the direction of the nanoparticles, regarding the positioning of the laser would allow the generation of better and more robust statistical models for the prediction of the heat and temperature that they will generate. By clustering nanoparticles, the heat generation of hyperthermia treatments can be accurately measured. This concentration of GNR nanoparticles (clusters) has a large effect on the temperature distribution. Lower concentrations result in smaller temperature gradients.

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